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BOZICEVIC, FIELD & FRANCIS LLP

200 Middlefield Road
Suite 200
Menlo Park, California 94025
Telephone (650) 327-3400
Facsimile (650) 327-3231

Date: February 7, 2002

To: 1650-60 Art Unit's Fax Number
Attention: **Examiner H. Robinson**
U.S. Patent and Trademark Office

Facsimile No.: (703) 305-7230

From: Pamela J. Sherwood, Ph.D., Reg. No. 36,677

Re: Supplemental Amendment/Response for US Patent Application Serial No. 09/341,505 for ASSAYS, AGENTS, THERAPY AND DIAGNOSIS RELATING TO MODULATION OF CELLULAR DNA REPAIR ACTIVITY

Message: Please see attached filing following this cover sheet.

Total number of pages, including this cover sheet: 8

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TRANSMITTAL FORM

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Total Number of Pages in This Submission: 7

Application Number	09/341,505
Filing Date	July 12, 1999
First Named Inventor	JACKSON, STEPHEN PHILIP
Group Art Unit	1653
Examiner Name	ROBINSON, H.
Attorney Docket Number	MEWE-005

ENCLOSURES (check all that apply)

- [ ] Fee Transmittal Form
  - [ ] Fee Attached
- [x] Supplemental Amendment / Reply
  - [x] After Final
  - [x] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Documents
- [ ] Response to Missing Parts/ Incomplete Application
  - [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Assignment Papers *(for an Application)*
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) ____
- [ ] After Allowance Communication to Group
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to Group *(Appeal Notice, Brief, Reply Brief)*
- [ ] Proprietary Information
- [ ] Status Letter
- [ ] Other Enclosure(s) *(please identify below):*

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual Name	PAMELA J. SHERWOOD, Reg. No. 36,677
Signature	Pamela Sherwood
Date	February 7, 2002

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Signature	Susan M. Alessi	Date	February 7, 2002

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Typed or Printed Name	Susan M. Alessi		
Signature	Susan M. Alessi	Date	02-07-2002

SUPPLEMENTAL RESPONSE TO APPLICANTS RESPONSE OF JANUARY 22, 2002 UNDER 37 C.F.R. § 1.116 Faxed to: Facsimile: (703) 305-7230 Box AF Assistant Commissioner for Patents Washington, D.C. 20231	Attorney Docket Confirmation No.	MEWE-005 5221
	First Named Inventor	Jackson et al.
	Application Number	09/341,505
	Filing Date	July 12, 1999
	Group Art Unit	1653
	Examiner Name	H. Robinson
	Title	ASSAYS, AGENTS, THERAPY AND DIAGNOSIS RELATING TO MODULATION OF CELLULAR DNA REPAIR ACTIVITY

Sir:

This response is responsive to the Final Office Action dated September 21, 2001 and Supplemental to Applicant's response of January 22, 2002. Enclosed herewith please find a Declaration under 37 CFR 1.132 by Dr. Stephen Jackson.

If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number MEWE-005.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: February 7, 2002

By: Pamela J. Sherwood
Pamela J. Sherwood
Registration No. 36,677

BOZICEVIC, FIELD & FRANCIS LLP
200 Middlefield Road, Suite 200
Menlo Park, CA 94025
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

#21

Declaration 3/21/02 lms.

Docket Number: MEWB005

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Jackson et al.
Serial No.	:	09/ 341,505
Examiner	:	Hope Robinson
Art Unit	:	1653
Filed	:	July 12, 1999
For	:	Assays, Agents, Therapy and Diagnosis Relating to Modulation of Cellular DNA Repair Activity

DECLARATION OF STEPHEN P. JACKSON

Sir :

I, Stephen P. Jackson, of 62 High St, Coton, Cambridge, CB3 7PL hereby declare and state THAT:

1. I am Professor of Biology at the University of Cambridge, Deputy Director of the Wellcome/CRC Institute of the University of Cambridge and Chief Scientific Officer of KuDOS Pharmaceuticals Limited, the company to whom the instant Patent Application has assigned been by the inventors. I am responsible for the co-ordination of research programmes being undertaken within KuDOS Pharmaceuticals Limited and by third parties on their behalf and I am a co-inventor on the instant Patent Application.

2. I have reviewed the specification and pending claims of the above-identified patent application, and in particular, the claims as amended in the Amendment and Response which I understand will accompany this Declaration. A copy of those claims is attached hereto as

Exhibit B. I have also reviewed the Office Action dated 21 September 2001. I understand that former claims 1-6, 19, 22 and 25 were rejected under 35 U.S.C. s 112 first paragraph on the grounds that the specification does not reasonably provide enablement for any person skilled in the art to make and use the invention commensurate with the scope of these claims and under 35 U.S.C. s 112 second paragraph as being indefinite for failing to point out and distinctly claim the subject matter which the applicant regards as the invention.

3. I make this Declaration specifically to address the teachings of the present specification. It is my opinion that the present specification describes the invention in sufficiently full, clear, concise and exact terms as to enable any person skilled in the art to make and use the claimed methods. It is also my opinion that the present claims point out and distinctly claim the subject-matter of the present invention.

4. XRCC4 was known to be involved in non-homologous end-joining (NHEJ) prior to the present invention (see, for example, Li et al (1995) Cell 83: 1079-1083), although no specific activity had been identified. DNA ligase IV was also known, although no function or role had yet been assigned to it.

5. In general, the specific binding of one protein to another is strong evidence of a functional relationship between the two proteins. The experimental data in Example 1 of the present specification demonstrates that XRCC4 binds to DNA ligase IV in cells in a specific and stoichiometric manner. Significantly, neither XRCC4 nor DNA ligase IV exists within the cell independently of the other. At the time of the invention, this data was persuasive evidence to workers in the field that DNA ligase IV, like XRCC4, played an important role in non-homologous end-joining (NHEJ). Moreover, the specification provided additional support for this conclusion in Example 2, in which the yeast DNA ligase IV homologue *LIG4* is shown to function in non-homologous end-joining (NHEJ). A skilled person would therefore understand from the data presented in the specification that DNA ligase IV played a role in DNA non-homologous end-joining (NHEJ) which was mediated by binding to XRCC4.

6. The XRCC4/DNA ligase IV interaction described in the present application was subsequently reported in the peer reviewed journals Current Biology and Nature (Critchlow (1997) Current Biology 7 588-698 and Grawunder (1997) Nature 388 (6641) 492-495; of

record). The finding that the XRCC4/DNA ligase IV complex is involved in non-homologous end-joining, as disclosed in the present specification and reported in these papers, has subsequently been confirmed in a range of published papers (see for example Grawunder et al (1998) Molecular Cell 2:477-484, Frank et al (1998) Nature 396:173-177, Riballo et al (1999) Current Biology 9:699-702; all of record) and is now generally accepted in the field.

7. Once two proteins have been found to bind to each other, it is entirely routine for a person of ordinary skill to determine whether a compound inhibits or enhances this binding. Any one of a range of well established methodologies may be used for this purpose. Whilst extensive investigations may be required to identify the two binding proteins, no undue experimentation is required to perform assay or screening methods once binding has been identified. Once a skilled person knows about that two proteins specifically bind, he is able to perform assay methods based on that binding. Such methods are simply the routine application of well established protocols in the field of molecular biology.

8. The specification therefore provides full technical enablement to the skilled person which allows the performance of assay methods for inhibitors of the binding of XRCC4 to DNA ligase IV . A skilled person would have no difficulty in carrying out such methods on the basis of the teaching of the present specification.

9. I hereby declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 16th January 2002

Stephen P. Jackson

EXHIBIT B

1. An assay method for a compound which inhibits the binding between XRCC4 (XR-1 Cell Complementing 4) and DNA ligase IV, or XRCC4 and DNA-PK_{CS}/Ku (DNA-dependent Protein Kinase catalytic subunit/Ku) , or XRCC4, DNA ligase IV and DNA-PK_{CS}/Ku, the method comprising the steps of:

(i) bringing into contact XRCC4, a test compound and one or more components selected from the group consisting of DNA ligase IV and DNA-PK_{CS}/Ku;

under conditions wherein, in the absence of said test compound being an inhibitor of binding, said XRCC4 binds to said one or more components selected from the group consisting of DNA ligase IV and DNA-PK_{CS}/Ku; and

(ii) determining binding between said XRCC4 and said one or more components selected from the group consisting of DNA ligase IV and DNA-PK_{CS}/Ku;

reduction or abolition in binding between said XRCC4 and said one or more components selected from the group consisting of DNA ligase IV and DNA-PK_{CS}/Ku being indicative that said test compound inhibits binding between XRCC4 and DNA ligase IV, or XRCC4 and DNA-PK_{CS}/Ku or XRCC4, DNA ligase IV and DNA-PK_{CS}/Ku.

2. An assay method for a compound which inhibits binding between XRCC4 and DNA ligase IV or XRCC4 and DNA-PK_{CS}/Ku, or XRCC4, DNA ligase IV and DNA-PK_{CS}/Ku, the method comprising the steps of:

(i) bringing into contact a test compound and a polypeptide selected from the group consisting of XRCC4, DNA ligase IV and DNA-PK_{CS}/Ku;

(ii) determining binding between said polypeptide and said test compound,

binding between said polypeptide and said test compound being indicative that said test compound inhibits binding between XRCC4 and DNA ligase IV or XRCC4 and DNA-PK_{CS}/Ku or XRCC4, DNA ligase IV and DNA-PK_{CS}/Ku.

3. An assay method for a compound which inhibits DNA ligase IV activity, the method including the steps of:

(i) bringing into contact DNA ligase IV and a test compound; and

(ii) determining DNA ligase activity in the presence and the absence of test compound,

a decrease in the activity in the presence relative to the absence of test compound being indicative that said test compound inhibits the activity of DNA ligase IV

4. An assay method according to claim 3 wherein the DNA ligase activity is determined in the presence of XRCC4.

6. An assay method comprising

(i) bringing into contact a test compound, DNA-PKcs/Ku and XRCC4; and

(ii) determining phosphorylation of said XRCCC4 in the presence and absence of test compound;

a decrease in phosphorylation in the presence relative to the absence of test compound being indicative that said test compound inhibits the phosphorylation of XRCC4 by DNA-PKcs/Ku.

19. A method comprising obtaining a compound which inhibits the binding between XRCC4 and DNA ligase IV, or XRCC4 and DNA-PKcs/Ku, or XRCC4 and DNA ligase IV and DNA-PKcs/Ku, employing a method according to claim 1 or claim 2; and, formulating said compound into a composition which comprises a pharmaceutically acceptable excipient.

22. A method comprising obtaining a compound which inhibits DNA ligase IV activity employing a method according to claim 3 and formulating said compound into a composition which comprises a pharmaceutically acceptable excipient.

25. A method comprising obtaining a compound which inhibits DNA-PKcs/Ku phosphorylation of XRCC4 employing a method according to claim 6 and formulating said compound into a composition which comprises a pharmaceutically acceptable excipient.